CHAPTER 1 INTRODUCTION

Since its first successful application in 1953 by John H. Gibbon, Jr, MD, (Nolan and Zacour, 1997) cardiac surgery with cardiopulmonary bypass (CPB) has been evolved to a higher level of increased understanding of physiology and pathophysiology of extracorporeal circuit design (Figure 1.1). In neonates and infants undergoing CPB, the effects of hypothermia, altered perfusion, haemodilution, acid-base management, embolization and the systemic inflammatory response remain a challenge. These are primarily related to their high ratio of surface area to body weight (Laurie, 1999), immature thermal autoregulatory (Laurie, 1999), smaller circulatory volume, immaturity of most organ systems at birth and increased capillary membrane permeability. Maintaining optimum level of blood gases for infant especially during hypothermic cardiopulmonary bypass may be corrected by pH-stat or alpha-stat strategy.

The pH-stat method has been adapted in this study to enhance cerebral protection for infant undergoing hypothermic condition during CPB for repair of congenital heart defects, by adding carbon dioxide gas to the oxygenator. pH-stat management may provide improved cerebral physiologic recovery following periods of hypothermia during CPB using instruments that might correct hypocapnia caused by hypocarbia. Open heart surgery needs the aid of heart-lung machine and involves cooling patients to a mild, moderate or deep hypothermic state. Carbon dioxide diffuses rapidly across blood brain barrier, reducing extracellular fluid pH and causing cerebral vasodilatation. Hypothermia reduces the metabolic rate and the rate of CO_2 production. On the other hand, hypothermia also increases the solubility of CO_2 in blood and decreases the partial pressure of CO_2 for a given CO_2 content of blood (Yong *et al*., 2007).

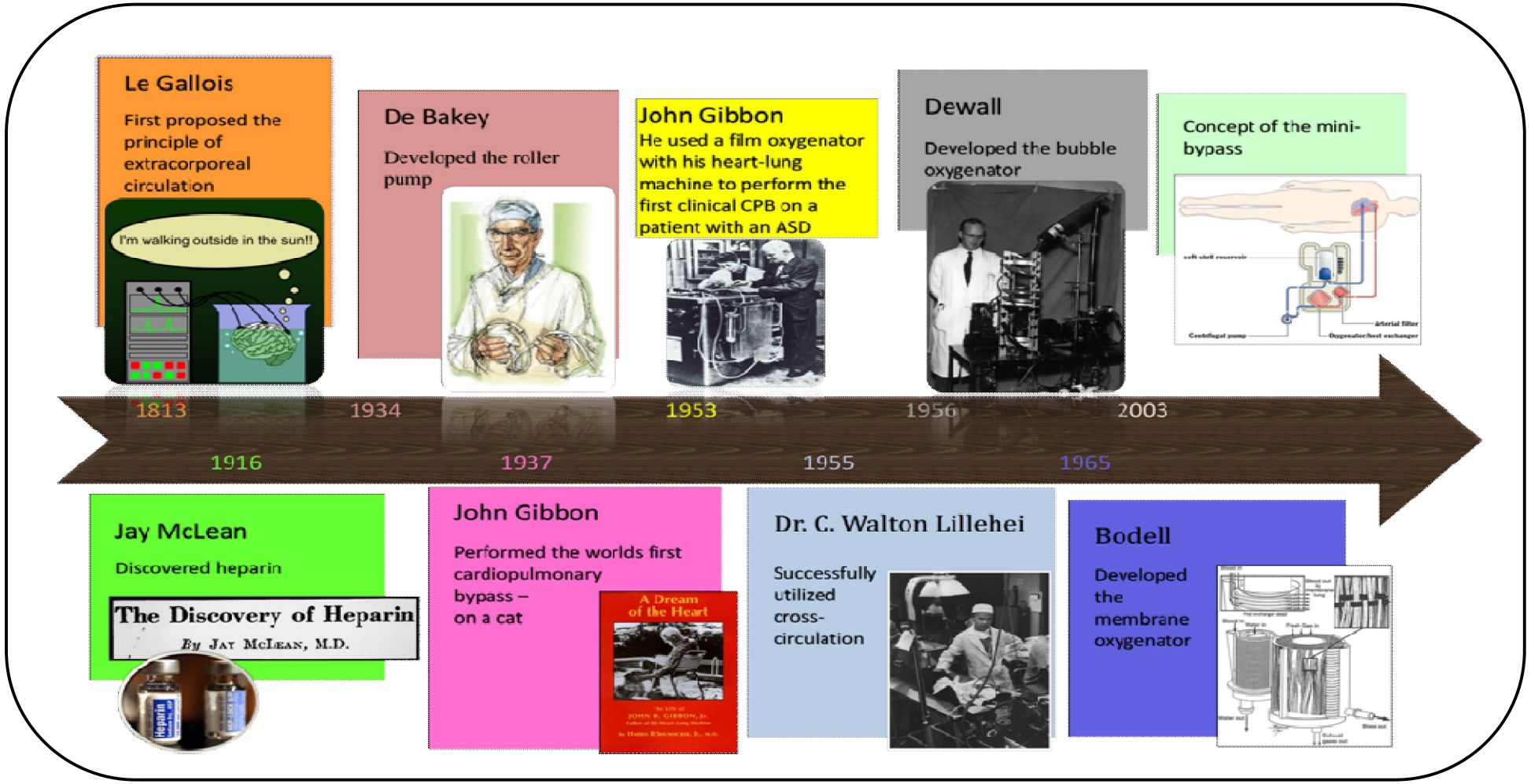

Figure 1.1: Key Developments in Extracorporeal Support.

Three different phase of CPB were explored; namely cooling, steady-state (stable), rewarming conditions in patients undergoing CPB. During CPB, desaturated blood drains from the right atrium to the venous reservoir via the venous line and is oxygenated by passive diffusion of oxygen through the semi-permeable membrane in the oxygenator. Removal of carbon dioxide from the blood depends on the sweep-gas flow rate, equilibration coefficient of oxygenator, and ventilation/perfusion (V/Q) ratio (Pybus *et al.*, 1991). Equilibrium between CO_2 production and consumption are reflected with the arterial partial pressure of carbon dioxide ($PaCO_2$). CO_2 exchange rate is highly dependent on sweep gas flow rate during CPB. However, for infant below 5kg the minimum gas sweep 0.1 L/min flushes out the CO_2 more than it elevates CO_2 within range 35 to 40 mm/Hg (pH-stat stand of view). For this reason carbogen usage may balance the CO_2 exchange rate in oxygenator during CPB especially during hypothermia.

The aims of this study are as follows:

- To assess whether carbogen usage to regulate the pH-stat management would increase the percentage of $PaCO_2$ and pH level falling within the reference range as compared to control group;
- To evaluate pH-stat management strategy with and without carbogen in infant undergoing hypothermic bypass;
- To investigate correlation between temperatures with arterial pCO_2 in pH-stat management for infant undergoing cardiopulmonary bypass (CPB).

CHAPTER 2 LITERATURE REVIEW

2.1 Hypothermia

Hypothermia is used for brain protection mainly because it reduces tissue metabolism and may cause a decrease in free radical activity (Bigelow *et al*., 1950; Phoon, 1993; Greeley *et al*., 1989; SP Wardle *et al*., 1997). Hypothermia, which is commonly used during CPB, can lead to decreased organ perfusion from vasoconstriction resulting, at least in part, from the reduction of CO_2 partial pressure (Yong *et al*., 2007). During cooling, the decreased kinetic energy associated with a lower temperature decreases the dissociation of all weak acids and bases in biologic solutions (Lennart *et al*., 2002). Thus, hypothermia results in a natural alkaline shift of blood pH (Lennart *et al*., 2002). However, in children the rate of blood flow to metabolic rate increases with hypothermia which in turn reduces cerebral oxygen consumption in an exponential way and blood flow in linear way (Laussen, 2002). Hypothermia aids in preventing calcium entry into the cell, restricts membrane permeability and generally results in a decrease in blood flow to all organs of the body (Laurie, 1999).

2.2 Oxygen and Carbon Dioxide Production and Consumption

The role of CO_2 management in cardiopulmonary bypass (CPB) has been extensively studied experimentally and in adult patients. But, there were no critical studies for temperature corrected values for arterial pH and CO_2, i.e. pH-stat, during hypothermia (Laussen, 2002). O_2 delivery to tissues is usually normalized by setting standard pump flow values that compensate for haemodilution; besides, inadequate O_2 delivery is balanced to a certain extent by increased O_2 extraction, so that further

adjustments to pump flow can be made on the grounds of O_2 consumption and venous blood O_2 saturation (Cavaliere *et al*., 1995; Harris *et al*., 1971; Alston *et al*., 1989). The CO_2 in the blood combines chemically with different moieties to form bicarbonate, the major carrier of CO_2 in blood, and to amino groups of proteins, primarily haemoglobin, and is not linearly related to the partial pressure of CO_2 (Glenn *et al*., 2008). CO_2 removal from tissues is more difficult to normalize since many factors affect the balance between CO_2 production and output, including respiratory quotient, gas solubility and changes in CO_2 stores in the body (Cavaliere, 2000). Based on the effect of CO_2 tensions on arterial, intracellular, and extracellular pH at hypothermic temperatures, two divergent blood gas management strategies have played an important role: alpha-stat (temperature uncorrected) and pH-stat (temperature corrected). Body surface area (BSA) can also be an estimation of the metabolic needs of tissues (O_2 consumption and CO_2 production) and, therefore, of the performance required by the oxygenator both for gas exchange and for blood flow.

2.3 Alpha-stat management

Two alternative strategies have been developed in response to the natural alkaline shift (Lennart *et al*., 2002). The term alpha-stat strategy indicates a pH management strategy in which the blood carbon dioxide is allowed to follow its thermodynamically mediated dissociation changes with hypothermia, which results in a decrease of hydrogen ion concentration [H^+] (decreased dissociation) and an increase of blood pH (alkaline shift) (Lennart *et al*., 2002). This means in clinical practice no carbon dioxide is added to the oxygenator gas to compensate for these changes in blood pH during cooling (Lennart *et al*., 2002). Alpha-stat application on perfusion aim is to maintain constant blood CO_2 content during open heart surgery. The alpha-stat method measures the blood gas sample at 37˚C regardless of the patient temperature.

Hypothermia will increase CO_2 plasma solubility in patient. To sustain constant CO_2 content during cooling more carbon dioxide must be removed than with pH-stat. To maintain constant CO_2 content, the gas sweep or ventilation rate will be higher than pH-stat.

2.4 pH-stat management

The alternative method of pH management during cardiopulmonary bypass is termed pH-stat (Lennart *et al.*, 2002). In this method, blood pH is maintained constant at decreasing temperatures. With the pH-stat strategy, 3 to 5% carbon dioxide (CO_2) is added to the oxygenator gas flow during hypothermic CPB to maintain a temperature corrected blood pCO_2 of 40 mmHg and a pH of 7.40 (Lennart *et al.*, 2002). In the 1960s and 1970s, the pH-stat strategy was used widely (Lennart *et al.*, 2002). In the 1980s, many institutions shifted toward the alpha-stat strategy for pH management mainly because of studies of cold-blooded vertebrates (Rahn *et al.*, 1975). pH-stat relevance on perfusion goal is to elevate constant pH and increasing CO_2 content during open heart surgery. The pH-stat method measures the blood gas sample at 37˚C then adjusts for the temperature change of the patient. pH stat corrects all blood gases to patient hypothermic temperature and not at 37˚C. Increasing levels of hypothermia and corresponding CO_2 plasma solubility will increase total CO_2 content in order to maintain temperature corrected pCO's of 40 mm/Hg.

2.5 Advantages and Disadvantages

There are theoretical advantages and disadvantages for both pH strategies (Lennart *et al.*, 2002) (Figure 2.1). Alpha-stat has been said to better preserve intracellular pH and enzyme activity (White, 1981). It has been argued that it better preserves autoregulation of cerebral vasculature and cerebral flow-metabolism coupling (Murkin *et al.*, 1987). One continuing reason for the popularity of alpha-stat in clinical practice is because no addition of carbon dioxide is required (Lennart *et al.*, 2002). Disadvantages of alpha-stat include less efficient and less homogeneous cooling and less reduction of oxygen consumption (Lennart *et al.*, 2002). Advantages of the pH-stat strategy include increased cerebral blood flow (CBF), more homogeneous cooling, greater reduction of oxygen consumption and increased tissue oxygen availability because of a shift in the oxyhemoglobin dissociation curve (Lennart *et al.*, 2002). On the other hand adding CO_2 to maintain normal pH has to be handled carefully because CO_2 solubility increases with hypothermia. This results in relative hypercarbia and acidemia. Arguments against pH-stat strategy have centred on the potential for impaired cellular function following reperfusion and associated increase in cerebral blood flow problem (Laussen PC.; 2002). The intracellular acidosis that develops during deep hypothermic cardiac arrest recovers more rapidly with pH-stat than with alpha-stat, and there is no evidence that such acidosis delays or prevents full brain recovery (Laussen, 2002).

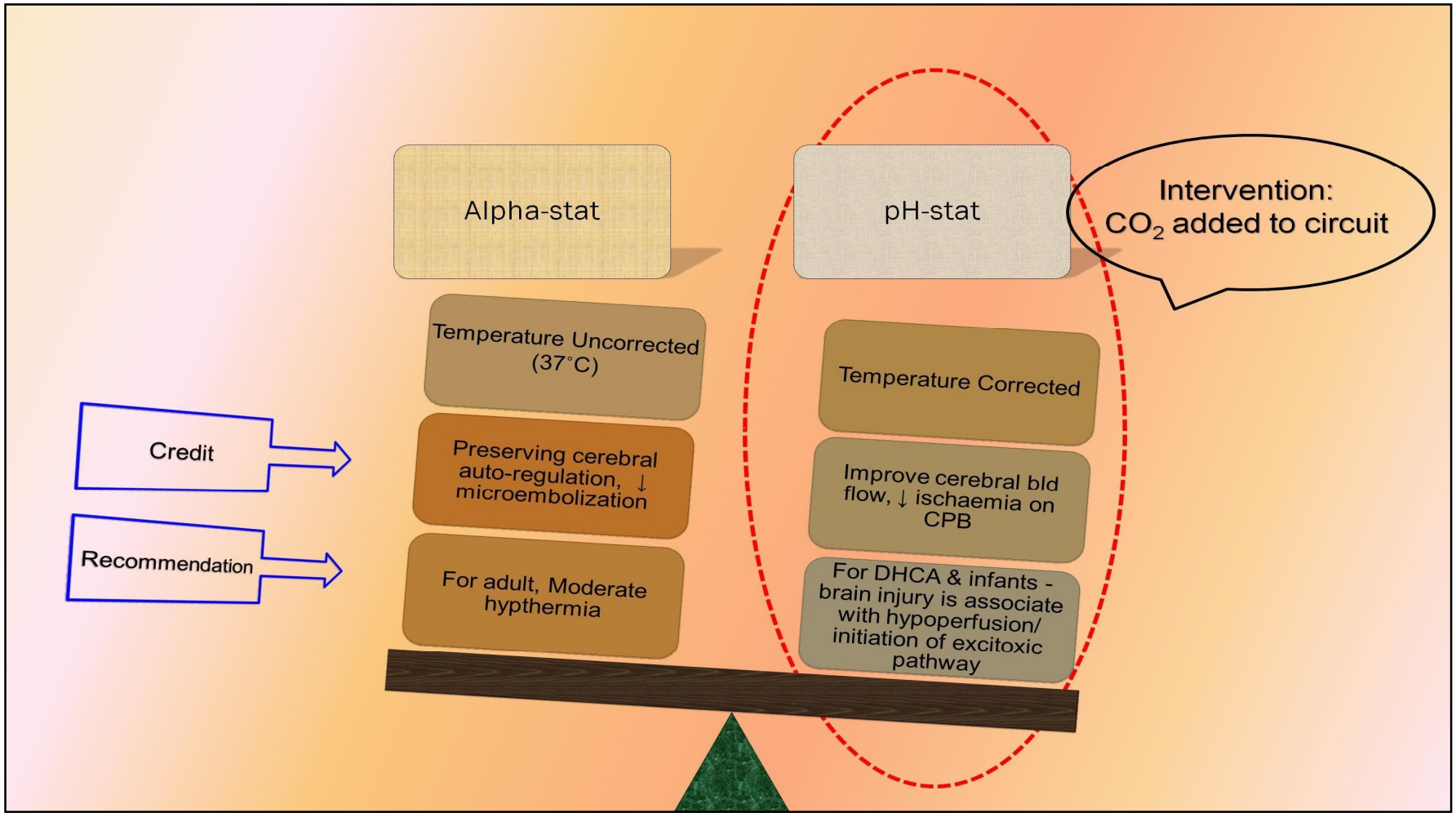

Figure 2.1: pH-stat in comparison with alpha-stat.

2.6 Gas Transfer in Membrane Oxygenator

Oxygenators are capable of performing many functions of native lung except for endocrine and biological transformation of humoral factor (Glenn *et al.*, 2008). Fundamental purpose of the oxygenator is to arterialize venous blood by removing excess carbon dioxide and increasing the partial pressure of oxygen (pO_2) (Glenn *et al.*, 2008). Membrane oxygenators can be divided into either microporous polypropylene (0.3 to 0.8 µm pores) or silicone rubber for the interphase between the gas and blood. Originally, oxygenators were constructed using a single silicone membrane. Hollow-fiber oxygenators were introduced in the 1970s (Dutton RC *et al.*, 1971). The hollow-fiber oxygenators have an increased gas transfer rate and are currently the standard model for all oxygenators. However, there is no agreement on the material used to construct them: – Oxygenators using hollow fibres made from silicone rubber, polymethylpentene (PMP), and polypropylene are commercially available. Of highest importance is the fiber material, but bundle design, including the geometry of the fiber bundle, fiber diameter, wall thickness, and packing density also contribute (J. Talor et al.; 2010). Capiox® RX05 (Terumo Cardiovascular System Co., Tokyo, Japan) or Baby RX™ (BRX), with a nonheparin biocompatible polymer coating ('X-coating®') (Figure 2.2) and Medtronic® Minimax Plus® Hollow Fiber Oxygenator (Medtronic Inc., Minneapolis, MN, USA) (Figure 2.3) are membrane oxygenators with microporous polypropylene hollow fibers. With microporous membranes, plasma-filled pores prevent gas entering blood but facilitate transfer of both oxygen and CO_2. Because oxygen is poorly diffusible in plasma, blood must be spread as a thin film (approximately 100 µm in thickness) over a large area with high differential gas pressures between compartments to achieve oxygenation. Diffusive qualities of membrane material determine the transfer of oxygen and carbon dioxide between phases (Glenn *et al.*,

2008). Areas of turbulence and secondary flow enhance diffusion of oxygen within blood and thereby improve oxyhemoglobin saturation (Drinker *et al*., 1969).

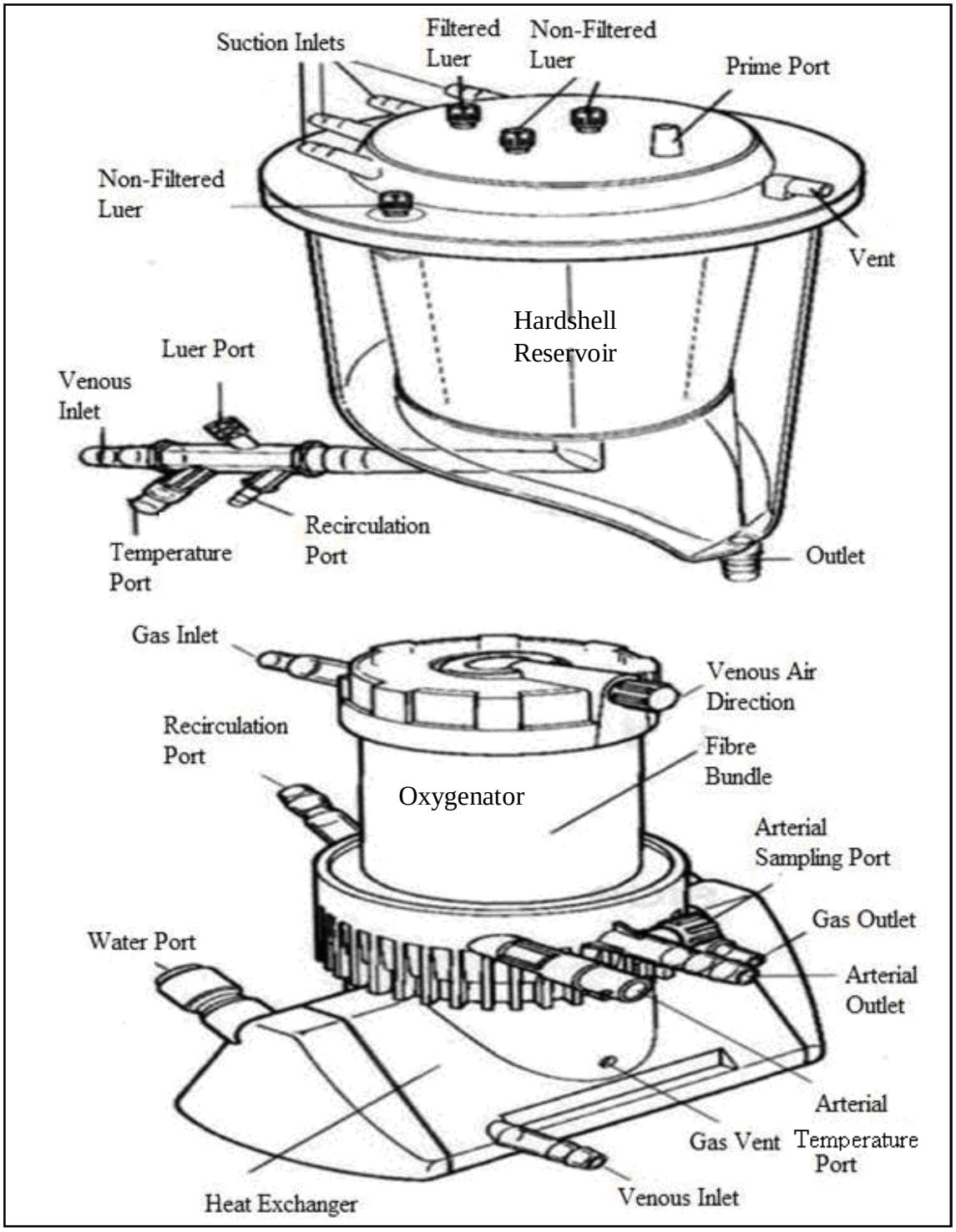

Figure 2.2: This picture is modified from Medtronic® MINIMAX PLUS® 3301 Hollow Fiber Oxygenator with Plasma Resistant Fiber (PRF) with Filtered Hardshell Venous Reservoir, Instruction for Use (Medtronic USA, Inc.; 2003).

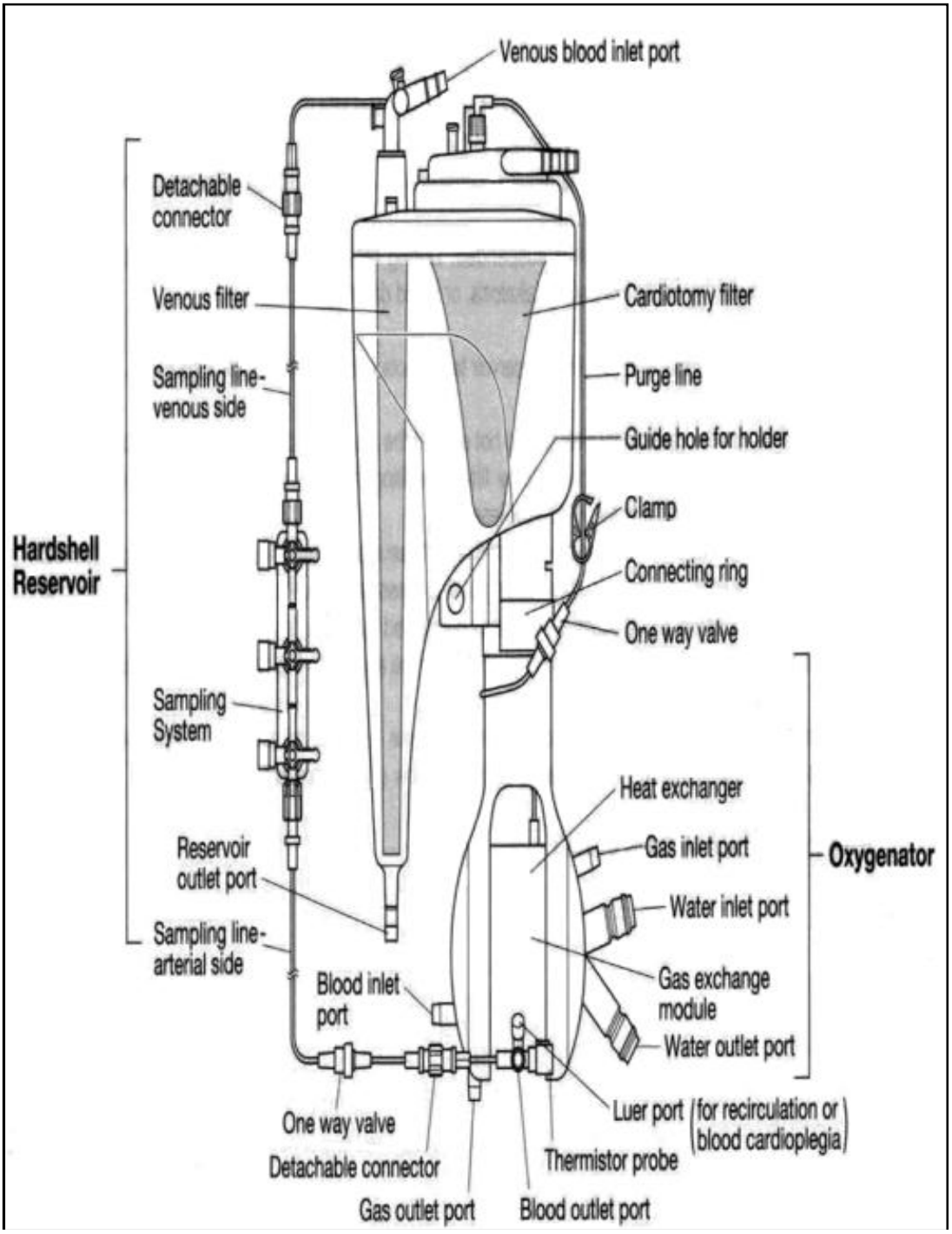

Figure 2.3: This picture is adapted from TERUMO® Hollow Fiber Oxygenator CAPIOX® RX 05 BABY-RX, Instruction for Use (Terumo Cardiovascular Systems; 2003).

Carbon dioxide is highly diffusible in plasma and easily exits the blood compartment despite small differential pressures across the membrane. With microporous membranes, plasma-filled pores prevent gas entering blood but facilitate transfer of both oxygen and CO_2. The most popular design uses sheaves of hollow fibers (120 to 200 µm) connected to inlet and outlet manifolds within a hard-shell jacket. The most efficient configuration creates turbulence by passing blood between fibers and oxygen within fibers. Blood flow through a hollow fiber oxygenator: through the fiber or around it (Glenn et al., 2008). Arterial PCO_2 is controlled by gas flow, and PO_2 is controlled by the fraction of inspired oxygen (FiO_2) produced by an air-oxygen blender. Modern membrane oxygenators add up to 470 mL of O_2 and remove up to 350 mL CO_2 per minute at 1 to 7 litres of flow with priming volumes of 220 to 560 mL and resistances of 12 to 15 mm Hg per litre blood flow. Most units combine a venous reservoir, heat exchanger, and hollow fiber membrane oxygenator into one compact unit. Flow regulators, flow meters, gas blender, oxygen analyser and gas filter are parts of the oxygenator gas supply system used to control the ventilating gases within membrane oxygenators. A phenomenon called wet lung may occur when water condensation occurs inside fibers of microporous membrane oxygenators with blood flowing exterior to the fibers. This may occur when oxygenators are used for a long period of time. If water condensation and/ or a decrease in PaO_2 and/or an increase in $PaCO_2$ are noted during extended oxygenator use, briefly increasing the gas flow rate may improve the performance. Increase gas flow rate, to 5 L/min for 10 seconds. Do not repeat this flushing technique, even if oxygenator performance is not improved. A minimum of 0.05 L/min oxygen gas flow or minimum V/Q 0.2 is needed when blood is circulated. Less than 0.05 L/min oxygen gas flow or V/Q less than 0.2 may result in inadequate gas exchange (Terumo Cardiovascular Systems; 2003).